

HIGH DOSES OF PENICILLIN IN THE TREATMENT OF GONORRHOEA

RESULTS OF TREATMENT CORRELATED WITH THE SENSITIVITY PATTERNS OF THE CAUSATIVE GONOCOCCAL STRAINS*†

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Gonococcal strains less sensitive to penicillin have been found in a high proportion of patients failing to respond to penicillin treatment (Curtis and Wilkinson, 1958; Reyn, 1961; Gjessing and Ødegaard, 1962a; Laird, 1963; Klaschka, Hanne-mann, and Ränike, 1963). In a series of female patients treated with two injections of 1·2 mega units procaine penicillin on consecutive days, the treatment failed in 4 per cent. of those infected with penicillin-sensitive strains and in 51 per cent. of those infected with strains resistant to streptomycin and less sensitive to penicillin. This difference was not found if the treatment consisted of four doses of 1·5 mega units given during 2 days (Rantasalo, Tam-milehto, and Wallenius, 1962).

A possible measure to prevent the spread of the less sensitive strains of gonococci would be the use in all cases of a dosage high enough to cure those infected with the less sensitive strains. The present paper reports the results of treating both female and male gonorrhoea patients with high doses of penicillin.

Material and Methods

The series consists of 565 female and 264 male patients (total 829) who were treated for gonorrhoea at the Municipal Out-Patients Clinic for Venereal Diseases, Helsinki, in 1961–63. Samples were taken from all patients for direct microscopy and for culture, and only those patients are included in this series whose cultures were positive for gonococci and who were also controlled by culture after treatment.

Samples were taken with charcoal-impregnated cotton swabs from the urethra of male patients and from the urethra and uterine cervix of female patients, and were put into Stuart's transport medium; they reached the laboratory on the same or the following day, and were cultured on heated horse-blood ("chocolate") agar enriched with 15 per cent. ascitic fluid and incubated at 36·5 to 37°C. in an atmosphere of about 10 per cent. CO₂ for 24 hours and then in the ordinary atmosphere for a further 24 hours. The organisms diagnosed as gonococci were those which formed typical colonies composed of oxidase-positive, Gram-negative diplococci that formed acid from glucose but not from maltose or laevulose and did not grow on plain nutrient agar at 37°C. The ability of a strain to ferment sugars was examined on HAP medium (Juhlin, 1963). Sensitivity to penicillin, streptomycin, tetracycline, and chloramphenicol was tested by the disk method and the diameters of the inhibition zones were converted to 50 per cent. inhibitory concentrations (IC₅₀ µg./ml.), using two Scandinavian reference strains (IV, IC₅₀=0·71 µg./ml. and VI, IC₅₀=0·0047 µg./ml.) as daily controls (Reyn, Bentzon, and Ericsson, 1963).†

The results of treatment were checked from one to four times, the first follow-up examination usually taking place one week after treatment. A failure was recorded if a positive culture was found within one month after treatment. A failure was regarded as a re-infection if there was a great difference in sensitivity between the gonococcal strains isolated before and after treatment (Schmidt and Larsen, 1962; Gjessing and Ødegaard, 1962b). The differences considered sufficient were:

- (1) Conversion of a streptomycin-resistant strain to a sensitive one, or *vice versa*;
- (2) At least a 10-fold change in penicillin sensitivity.

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‡ Details of the techniques of culture and sensitivity determination are to be found in "Metodik för odling och resistensbestämning av gonokocker". Karolinska Sjukhuset, Stockholm.

Results

Results of Different Treatment Schedules

The treatment schedules and results are summarized in Table I.

Females.—The cure rate achieved by one injection of procaine penicillin in female patients rose from 66 per cent. with 1·2 mega units to 81 per cent. with 3 mega units. With one injection consisting of 3 mega units di-penicillin (0·75 mega units sodium penicillin G and 2·25 mega units procaine penicillin G), the cure rate was still better (91 per cent.).

With two injections of 1·2 and 3 mega units procaine penicillin on consecutive days the cure rates were 83 and 91 per cent. respectively. Two injections of 3 mega units di-penicillin gave the best result, a 94 per cent. cure rate.

Males.—3 mega units procaine or di-penicillin gave cure rates of 94 and 95 per cent. respectively. All of 22 male patients treated with two injections of 3 mega units procaine penicillin G were cured, but the numbers concerned are very small.

Correlation of Results with Penicillin Sensitivity

Females.—Fig. 1 presents the results of different treatment schedules in female patients.

PENICILLIN-SENSITIVE STRAINS.—Those infected with penicillin-sensitive gonococcal strains ($IC_{50} \leq 0\cdot032 \mu\text{g./ml.}$ ($MIC \leq 0\cdot1 \text{ I.U./ml.}$)) showed a mean failure rate of 5·4 per cent. Higher failure rates were found when the patients were given only 1·2 or 3 mega units procaine penicillin.

LESS SENSITIVE STRAINS.—Many more failures occurred among patients infected with gonococcal strains less sensitive to penicillin ($IC_{50} > 0\cdot032 \mu\text{g./ml.}$), in whom the mean failure rate was 22 per cent.

The results showed a clear correlation with the degree of penicillin resistance of the infecting strains. In the whole female series, failure rates of 37, 21, and 10 per cent. were found among patients infected with gonococcal strains giving IC_{50} values of $\geq 0\cdot36$,

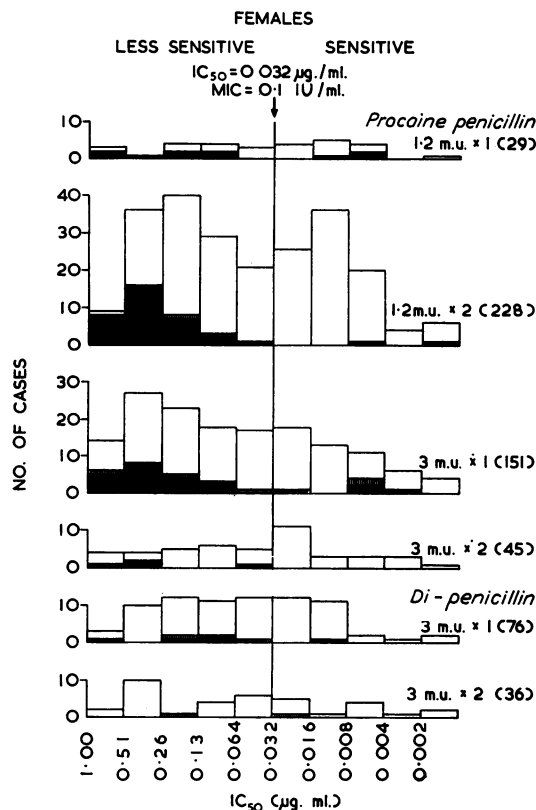


FIG. 1.—Results of six penicillin treatment schedules in 565 female patients, according to sensitivity to penicillin of causative gonococcal strains, the middle line indicating the boundary between the sensitive and less sensitive groups.

White: Cured;

Shaded: Strain changed between treatment and follow-up examination = Obvious re-infection;

Black: Failure (or re-infection with strain of similar sensitivity).

0·26–0·18, and 0·13–0·045 $\mu\text{g./ml.}$, respectively. Fig. 1 shows that the results were better when the dose of penicillin was increased, and the best results were obtained by treating the patients with high doses of di-penicillin.

TABLE I
RESULTS OBTAINED WITH DIFFERENT TREATMENT SCHEDULES IN THE WHOLE SERIES OF 829 PATIENTS

Treatment Schedule			Patients					
Type of Penicillin	Daily Dose (mega units)	No. of Doses Given	Female (565)			Male (264)		
			Total	Failures		Total	Failures	
				No.	Per cent.		No.	Per cent.
Procaine penicillin G ..	1·2	1	29	10	34	—	—	—
		2	228	38	17	—	—	—
	3	1	151	29	19	169	10	6
		2	45	4	9	22	—	—
Di-penicillin	3	1	76	7	9	73	5	7
		2	36	2	6	—	—	—

Males.—All the male patients were treated with high doses of penicillin. Fifty patients with penicillin-sensitive strains and 119 with less sensitive strains were treated with one injection of 3 mega units procaine penicillin, the failure rates being 0 and 8 per cent. respectively. 31 patients with penicillin-sensitive strains and 42 with less sensitive strains treated with one injection of 3 mega units di-penicillin gave four failures and one failure respectively (Fig. 2).

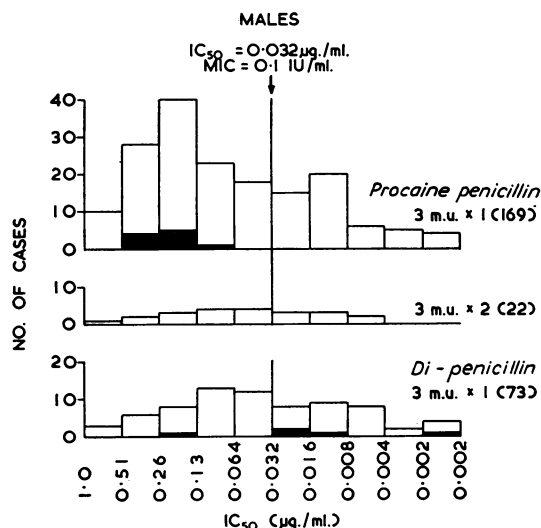


FIG. 2.—Results of three penicillin treatment schedules in 264 males, according to sensitivity to penicillin of causative gonococcal strains, the middle line indicating the boundary between the sensitive and less sensitive groups.

White: Cured;
Shaded: Strain changed between treatment and follow-up examination = Obvious re-infection;
Black: Failure (or re-infection with strain of similar sensitivity).

Resistance to Streptomycin

Sensitivity determinations were made on the 829 gonococcal strains isolated before treatment, and 255 strains (30.8 per cent.) were found to be fully resistant to streptomycin. Only 2.8 per cent. of the penicillin-sensitive strains were resistant to streptomycin, in contrast to 48.1 per cent. of strains less sensitive to penicillin (Table II).

TABLE II
PENICILLIN AND STREPTOMYCIN SENSITIVITY OF 829 GONOCOCCAL STRAINS ISOLATED BEFORE TREATMENT

Sensitivity to Penicillin	Sensitivity to Streptomycin		Total
	Sensitive	Resistant	
Sensitive	309	9	318
Less sensitive	265	246	511
Total	574	255	829

Females.—The results in the female patients infected with streptomycin-resistant or streptomycin-sensitive strains of gonococci are presented in Fig. 3. Those infected with strains less sensitive to penicillin and resistant to streptomycin had a failure rate of 45.3 per cent. with 3 mega units or less of procaine penicillin. Those infected with strains less sensitive to penicillin but sensitive to streptomycin had a failure rate of only 10.9 per cent. with the same dosage.

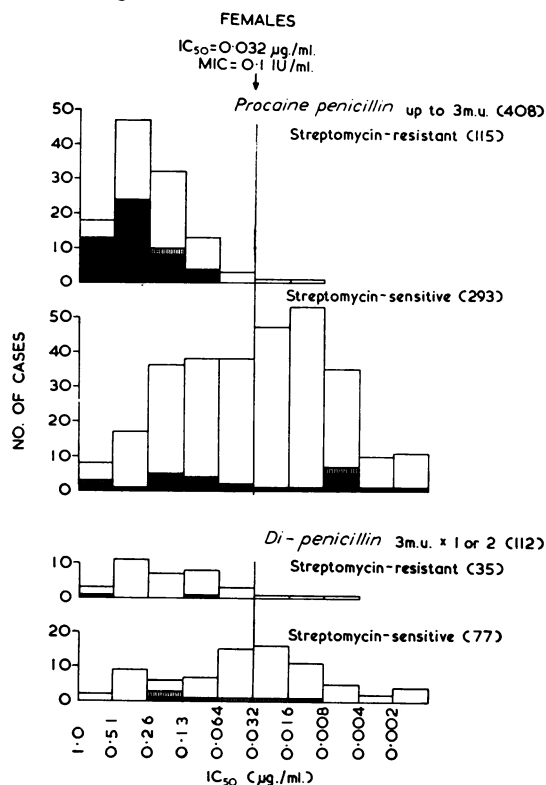


FIG. 3.—Results of procaine penicillin and di-penicillin treatment of 520 females, according to streptomycin sensitivity of gonococcal strains, and penicillin sensitivity of causative gonococcal strains.

White: Cured;
Shaded: Strain changed between treatment and follow-up examination = Obvious re-infection;
Black: Failure (or re-infection with strain of similar sensitivity).

Di-penicillin in one or two doses of 3 mega units gave good results both in patients infected with strains less sensitive to penicillin and resistant to streptomycin (6.3 per cent. failure rate) and in those with strains less sensitive to penicillin but sensitive to streptomycin (12.8 per cent. failure rate).

Males.—Male patients infected with strains less sensitive to penicillin and resistant to streptomycin had a failure rate of 11.3 per cent., and those with strains less sensitive to penicillin but sensitive to

streptomycin had a failure rate of 5.3 per cent., 3 mega units procaine penicillin G being used in each group. This difference was not found when 3 mega units di-penicillin were given.

Discussion

The number of gonococcal strains less sensitive to penicillin has increased markedly during the last decade, and has been the cause of many treatment failures. In the present series 61.6 per cent. of gonococcal strains were less sensitive to penicillin ($IC_{50} > 0.032 \mu\text{g./ml.}$).

Results of Treatment Correlated with Penicillin Sensitivity

Females

PENICILLIN-SENSITIVE GONOCOCCI.—The cure rates were about the same irrespective of the treatment used. Only procaine penicillin in doses of 1.2 and 3 mega units was not quite so effective as the other schedules.

GONOCOCCI LESS SENSITIVE TO PENICILLIN.—The cure rates varied greatly according to the dose, mode of administration, and type of penicillin. They declined with decreasing doses of penicillin, and one-half of the treatments failed with the smallest dose used. Thus one dose of 3 mega units procaine penicillin gave slightly better results than two doses of 1.2 mega units on consecutive days. These schedules failed in one-fourth of the cases.

The best results were obtained with di-penicillin (0.75 mega units sodium penicillin G and 2.25 mega units procaine penicillin G) given in two doses of 3 mega units on consecutive days, only two "failures" which were in fact obvious re-infections being observed with this schedule.

In comparing the results of treatment, no effort has been made to distinguish clinically between re-infections and true failures. Sexual contact between treatment and follow-up examination cannot by itself be regarded as an indication of re-infection, but the determination of the sensitivity of the gonococcal strains to antibiotics provides a means of distinguishing between re-infection and failure of treatment in some cases. A marked difference in the sensitivity patterns of gonococcal strains isolated from the same patient before treatment and at the follow-up examination indicates re-infection, but on the other hand, a similarity between the sensitivity patterns of isolated strains does not exclude re-infection. According to the criteria stated above under "Methods", eleven (1.9 per cent.) of the female patients were classed as re-infections, but they can represent only a part of the true number of

re-infections. The mean failure rate of all females infected with penicillin-sensitive strains of gonococci was 5.4 per cent., and this was probably near the true rate of re-infection. It thus seems that, with the smallest dose used (1.2 mega units), the 20 per cent. failure rate in those infected with penicillin-sensitive gonococci was too great to be caused by re-infections only, but the number of cases involved is very small.

Males.—The male series consists of patients treated with high doses only. It seems probable that nearly all male patients can be cured with 3 mega units procaine or di-penicillin.

Comparison of Female and Male Series

The results obtained with 3 mega units procaine penicillin show a definite difference between the sexes. There were about 16 per cent. failures in the female series and 5 per cent. in the male series. It might be thought that there would be more re-infections among women than men, but this is not very probable. Because gonorrhoea is not so noticeable in females as in males, the disease may be more advanced at the time of treatment in females than in males. Although complications, such as gonococcal salpingitis, are not diagnosed in the routine examination for venereal diseases, a further observation favours this assumption. During the summer of 1963, gonococci were isolated from nearly 10 per cent. of women diagnosed as cases of salpingitis at a gynaecological clinic in Helsinki. Another possibility is that the same dose of penicillin gives a higher concentration in the male urethra than in the vagina. Thus phagocytized gonococci may possibly survive in the vagina and later cause a "new" infection.

Streptomycin-Resistant Gonorrhoea

The relative number of streptomycin-resistant strains varies in different countries (Alergant, 1958; Roiron, Rasetti-Nicod, and Durel, 1961; Ringertz, 1961; Reyn, 1963); 30.8 per cent. of all strains isolated before treatment in the present series were resistant to streptomycin. Sensitivity to streptomycin gives a criterion whereby the gonococcal strains may be divided into two distinct types:

(1) *Streptomycin-Sensitive.*—53.8 per cent. were sensitive to penicillin.

(2) *Streptomycin-Resistant.*—Only 3.5 per cent. are sensitive to penicillin.

FEMALES.—The results of treatment showed a striking difference. Only 55 per cent. of female cases infected with gonococci less sensitive to penicillin and resistant to streptomycin were cured by up to 3 mega units procaine penicillin. In contrast to this, 89 per cent. of cases infected with strains less

sensitive to penicillin but sensitive to streptomycin were cured by the same doses. This difference was not found in patients who were treated with one or two doses of 3 mega units di-penicillin. Because the patients treated at the clinic have not essentially changed during the study period, the great difference observed when the lower doses of procaine penicillin were used must be due to true failures of treatment.

In females with streptomycin-sensitive gonorrhoea, the cure rates of those infected with gonococcal strains sensitive or less sensitive to penicillin and treated with up to 3 mega units procaine penicillin were 93 and 89 per cent. respectively.

The results of treatment show a markedly better correlation with streptomycin-sensitivity than with penicillin-sensitivity, but our findings are in sharp contrast to that of Miller and Bohnhoff (1945) that a gonococcal strain artificially made resistant to penicillin did not at the same time change its sensitivity to streptomycin.

Treatment of Gonorrhoea

Gonorrhoea must be treated on the basis of clinical and microscopical examinations, and treatment must not be delayed until the results of sensitivity determinations are known. Treatment must be short and effective to prevent spread of infection, and the dosage must be adequate to cure the most resistant strains of gonococci.

Since about one-fourth of the gonococcal strains isolated in Helsinki are resistant to streptomycin, this drug cannot be recommended. About 10 per cent. of the strains studied were less sensitive to tetracycline, but not one showed a lowered sensitivity to chloramphenicol. These antibiotics should be reserved for possible penicillin failures and should not be used in routine treatment.

Being relatively effective, harmless, and cheap, penicillin is still the drug of choice in the treatment of gonorrhoea, and a suitable dosage schedule cures practically all cases.

In this study, the best results in females were obtained by two injections of 3 mega units di-penicillin on consecutive days. One injection of 3 mega units procaine or di-penicillin cured practically all the male patients. No side-effects were encountered in this study, nor in that of Knudsen and Perdrup (1963).

Summary

829 cases of gonorrhoea (565 women and 264 men) were treated with penicillin, the total dose ranging from 1.2 to 6 mega units.

In patients infected with penicillin-sensitive gonococcal strains, the results were good irrespective

of the treatment schedule. In patients infected with gonococcal strains less sensitive to penicillin, the results were better when the dose of penicillin was increased.

Gonococci less sensitive to penicillin may be divided into two groups according to their sensitivity to streptomycin. The lower doses of procaine penicillin were less effective in patients with gonococci less sensitive to penicillin and resistant to streptomycin than in patients with gonococci less sensitive to penicillin but sensitive to streptomycin.

This difference was not observed when 3 or 6 mega units di-penicillin (0.75 mega units sodium penicillin G plus 2.25 mega units procaine penicillin G) were given.

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La blennorragie traitée par des doses fortes de pénicilline

RÉSUMÉ

On traita 829 cas de blennorragie (565 femmes et 264 hommes) avec 1.2 à 6 m.u. de pénicilline.

Les malades atteints d'organismes sensibles à la pénicilline furent guéris malgré le régime employé; chez ceux atteints de gonocoques moins sensibles, les résultats furent meilleurs avec les plus fortes doses de pénicilline.

Les gonocoques moins sensibles peuvent être divisés en deux groupes selon leur sensibilité à la streptomycine: les petites doses de pénicilline furent moins efficaces contre les gonocoques non seulement moins sensibles à la pénicilline mais aussi résistants à la streptomycine.

Cette différence disparut quand on donna 3 ou 6 m.u. de di-pénicilline (c'est à dire 0.75 m.u. de sodium pénicilline G + 2.25 m.u. de procaine pénicilline G).